PRIMARY ENDOTHELIOMA OF CERVICAL LYMPH-NODES*

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Although the medical profession generally thinks of primary endothelioma of cervical lymph-nodes as almost a curiosity, because of its rarity, Ewing, as early as 1913, and Jean Oliver since then, have asserted that the disease actually is much more prevalent than is commonly supposed. I personally have recognized it in only one instance, and then by biopsy, and in that case the disease resulted fatally. This one experience has sufficed to convince me that an early diagnosis of the disease (which I now realize would have been possible in that case), followed by a complete extirpation of it surgically while the condition is still local, will reduce fatality. At this time it is possible to recognize the disease only by biopsy, and to do so in that manner requires the services of a highly competent pathologist. Since it is at least possible histologically to differentiate the disease now, it can reasonably be expected that in due course it will become possible clinically to recognize the disease. Accordingly, the little I have by experience learned of the disease I propose to incorporate in this paper, in the hope it will be of service to some one who eventually can develop and publish a clinical picture of the disease.

Before reporting the solitary case that has come under my observation, it is proper briefly to summarize the published data on this subject. In 1869, the term "Endothelioma" was introduced by Golgi. For a long time afterward it was a debated question whether tumors actually originated in endothelium.

In 1880, Chambard described a primary cancer of lymph-nodes originating in endothelial cells, and in consequence he may properly be called the discoverer of primary endothelioma of the lymph-nodes. In his report he described a local form involving one node or one chain, and a generalized form that quickly resulted fatally. Thenceforth, and until 1913, primary endothelioma of the lymph-nodes was simply a medical curiosity having virtually nothing but theoretical interest.

In 1913, Ewing published a monograph entitled "Endothelioma of Lymph-nodes" reporting a series of cases, and with that paper the subject first acquired clinical importance. He somewhat boldly asserted that the disease is a rather common neoplasm, differing histologically, anatomically and even clinically from all other diseases, and especially secondary carcinoma, lymphosarcoma and Hodgkin's disease, which are the diseases with which it is still most often confused.

* Read before the Southern Surgical Association, December 15, 1926.

In consequence of the studies and reports of Ewing, Oliver, and others, we now know definitely that primary endothelioma is actually a distinct disease somewhat frequently arising in the lymph gland structure in the neck, the axilla, and the groin. We know, too, that at its inception and thereafter for a varying length of time it is occasionally a truly local condition admitting of complete cure if it involves accessible glands susceptible to surgical extirpation. We further know that the disease eventually becomes generalized and is then necessarily fatal, and as a consequence, the sooner its existence is recognized and it is treated, the more favorable will the prognosis be.

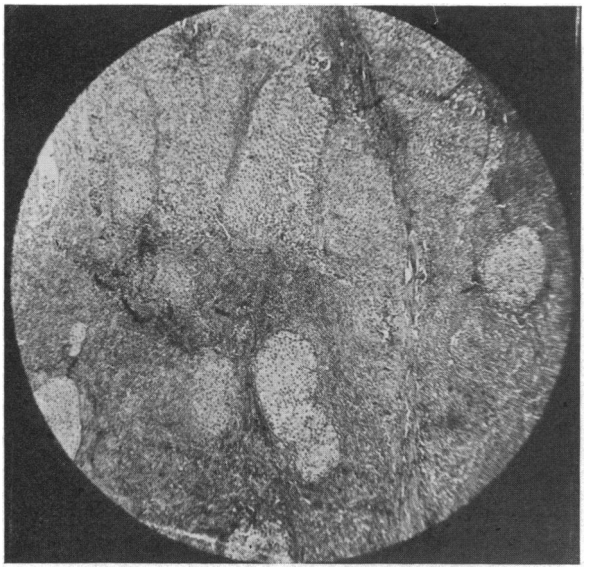

FIG. 1.—Primary endothelioma of cervical lymph-nodes. Low power, showing multiple foci of tumor tissue surrounded by intact lymphoid tissue of the lymph-node.

Although we have all this theoretical knowledge, its application in practice is one of the most difficult tasks confronting the surgeon. Primary endothelioma of cervical lymph-nodes has been, and can be, definitely differentiated. However, in many respects its manifestations are closely similar to those in other diseases, notably in acute infectious adenitis, tuberculosis, syphilis secondary lymphosarcoma, and Hodgkin's disease, and clearly to differentiate it from them all requires painstaking collaboration of diagnostician, pathologist, and surgeon.

Acute infectious adenitis of cervical lymph-nodes usually manifests itself in tonsillar infection, abscessed teeth, and ulcer of the scalp, or of the mucous membrane of the mouth or pharynx. The presence of infection in any of these specified areas with reasonable certainty thus explains a glandular enlargement in the cervical region.

Tuberculosis, when manifested in the cervical lymph-nodes, appears first in the sub-maxillary lymph-nodes, and soon afterwards the cervical glands in both sides of the neck become enlarged and continue to grow slowly, and the postcervical, supraclavicular and scapular systems and the bronchial lymph-nodes become affected. Associated rise in temperature and tenderness in the glands, which never characterize primary endothelioma of the cervical lymph-nodes, commonly concur in the presence of tuberculosis. In tuberculosis too, the superficial cervical glands have a tendency to caseation and sinus formation.

For differentiation of this disease and syphilis, a Wassermann usually suffices.

In secondary carcinoma, the primary lesion is usually located in the mouth or pharynx, and where the primary lesion is so located secondary carcinoma can with reasonable safety be diagnosed.

The real test of diagnostic skill lies in differentiating primary endothelioma of cervical lymph-nodes from Hodgkin's disease and lymphosarcoma of the cervical lymph-nodes.

Hodgkin's disease almost invariably manifests itself first in the lymph glands of one or both cervical regions and quickly thereafter a general adenopathy succeeds. The affected glands remain discrete but become enlarged. This disease is thought to be due to infection and for this reason it may become very painful early in the course of the disease. Metastasis to the viscera with resulting pressure symptoms is a common phenomenon in the course of the disease. Though chronic, this disease is characterized by remissions. Surgery is futile in its treatment and the disease terminates fatally at the end of two and one-half or three years.

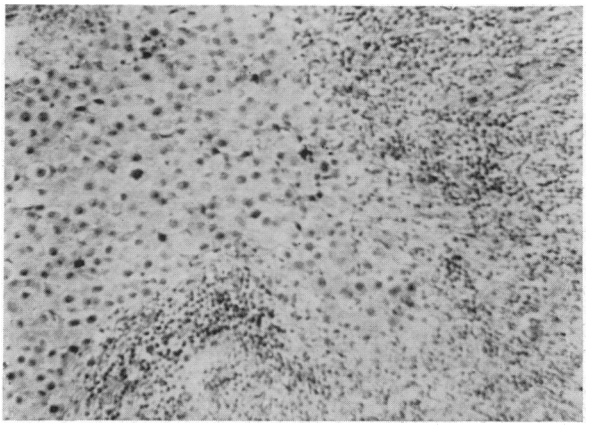

FIG. 2.—High power, showing areas of lymphoid tissue adjoining the endothelioma and giving a comparison in size and staining properties of the tumor cells with the persisting lymphoid cells.

Primary endothelioma of cervical lymph-nodes manifests itself first in either the superficial or deep lymph glands of the anterior or posterior cervical regions just as Hodgkin's disease does. Unlike that disease, it invariably manifests itself unilaterally and general adenopathy does not succeed, at least until the late stages. Although the glands remain discrete and become enlarged they do not become painful until the late stages of the disease. Metastasis to the viscera is an extremely rare phenomenon. Remissions do not characterize the disease, but it is consistently progressive. Surgery, while futile and even aggravative of malignancy in the advanced stages of the disease, may in its early stages accomplish a complete cure.

Lymphosarcoma of the cervical lymph-nodes is easily and commonly confused with both Hodgkin's disease and primary endothelioma of cervical lymph-nodes. Between it and the last named disease instant clinical differentiation is simply impossible as the two have almost identical clinical history and physical findings. Fortunately in the early stages of both diseases similar courses are run and to the same treatment both should be subjected. However, lymphosarcoma of the cervical lymph-nodes tends early to involve the

glands of both sides of the neck and to metastasize first to the supraclavicular regions and then to the mediastinum, and thus, and thus alone, will extended clinical observation admit of differentiation of the two diseases. Such differentiation, while academically interesting, necessarily comes too late to be practically helpful. In consequence, biopsy alone in our present state of knowledge accomplishes any practicable differentiation of these two diseases, and is the only really reliable basis for diagnosis where the presence of either of the three is suspected, and where such presence is suspected, the removal of a gland or the tumor for microscopic section and diagnosis should be made at the earliest possible moment.

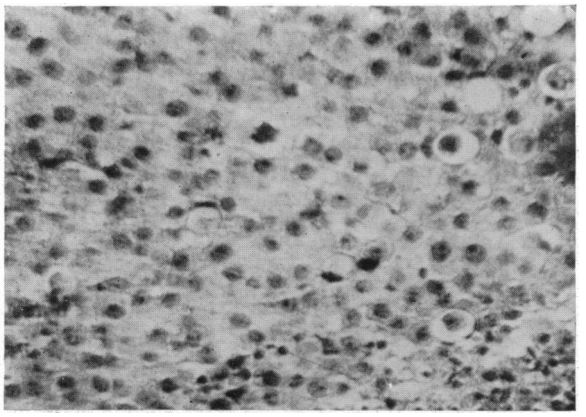

FIG. 3.—High power, showing details of the tumor cells.

If the microscope reveals endothelioma, the patient should if possible promptly be subjected to a radical block dissection of the cervical glands, and if he is, there is a fair chance of curing him. Of course, in lymphosarcoma, Hodgkin's disease and secondary carcinoma, surgery avails little, if indeed any. It is highly important to note that even by microscopic examination the differentiation in many cases is extremely difficult.

Among the highly distinguished students in this general field is Dr. Wm. B. Coley of New York, and as an evidence of the difficulties involved in diagnosing this disease I cannot forbear taking the liberty of quoting at length from a purely personal communication recently received from him. In part he says:

> In my opinion, based on an observation of a clinically considerable number of cases of tumors of the lymph glands, it is impossible to make a differential diagnosis between endothelioma and lymphosarcoma. Also, I believe in most cases it is extremely difficult to differentiate Hodgkin's disease from lymphosarcoma, not only clinically, but often microscopically as well. I have had cases in which one pathologist has classified the disease as lymphosarcoma, and another pathologist of equal standing has called it Hodgkin's disease. In some of my own cases a microscopical diagnosis of lymphosarcoma has been made at one time, and a little later on, the same pathologist has called it endothelioma. Cases in which it is possible to make a diagnosis of primary endothelioma of the cervical lymph glands, I believe, must be extremely rare.
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> One of the few cases that I recall in my own experience, in which a definite pathological diagnosis of primary endothelioma of the cervical lymph glands had been made, was seen clinically by one of the leading surgeons of Chicago, who pronounced it definitely inflammatory gland from infected teeth. The patient had a number of teeth extracted, without benefit. The surgeon still believing in the correctness of his diagnosis, sent the patient south for a number of months. When he returned, it was found that the

gland had increased considerably in size; it was then removed, and proved to be a primary endothelioma of the cervical lymph glands. In spite of thorough surgical removal, it recurred promptly. When the patient consulted me, he had a hopelessly inoperable malignant tumor involving the left cervical region as far as the clavicle. In spite of radium and toxin treatment, the disease gradually spread by infiltration, until it involved a large part of the pectoral region as well as the scapular and subscapular region, forming a huge tumor with an area of ulceration in the centre. At the end of a year and one-half, it killed the patient by exhaustion.

The foregoing quotation demonstrates the impossibility of clinical diagnosis and is a caveat of the unreliability of microscopic section as a basis for diagnosis of this disease. Notwithstanding his profound respect for Doctor Coley's matured judgment, the writer believes that microscopic section by a competent pathologist does admit of the definite diagnosis of the disease.

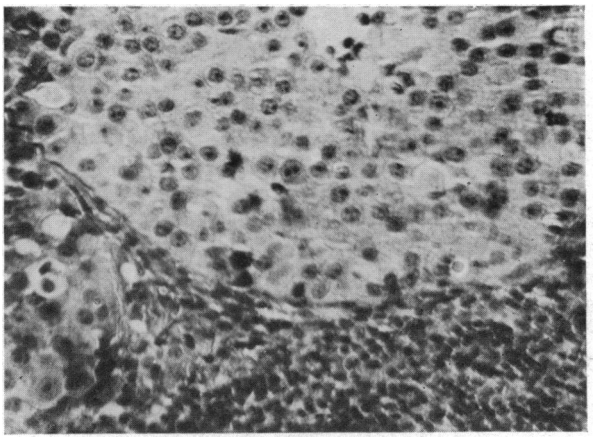

FIG. 4.—High power, showing margin of the tumor mass and the adjoining lymphoid cells.

On section the nodes present a moist, firm, friable, grayish-white, smooth surface that changes with variance in the degree of fibrosis or necrosis. The capsule is apparently intact, somewhat thickened, and infiltrated with lymphoid cells. The lymphoid structure of the node is largely lost, although there are areas of fairly dense lymphoid structure, with small blood-vessels, connective tissue cells and large endothelial cells of the same type that make up the main part of the new growth. The general structure is alveolated, the alveolar walls being of various thicknesses of connective tissue cells in all stages and carrying small blood-vessels. The contents of the alveoli are typically large rounded or polyhedral cells with fairly definite cell outlines and nucleus of vesicular type, with prominent basic staining nucleoli, occupying from one-half to three-fourths of the cell. The cytoplasm of the cell is clear. The alveoli are of various sizes and the contained cells appear to spring from the lining. In the centre of the alveoli, particularly the larger, the cells are shrunken, with opaque, deep acid-staining cytoplasm and small dense nuclei (pyknotic). Occasionally there is a central blood-vessel from around which the endothelial cells radiate, giving the appearance of perithelioma, these, however, seem to be simply projections of ruptured alveolar walls as rupture seems to have occurred frequently in the distended alveoli. In some areas the cells are flattened and dense, as from pressure, giving the appearance of carcinoma. The foregoing is the typical and general appearance of primary endothelioma of lymph-nodes as revealed by the microscope.

If through biopsic diagnosis the existence of primary endothelioma of cervical lymph-nodes is once established, choice must be made between two courses that alone are available as methods of treatment: palliation by X-ray, radium, and Coley's toxins, or extirpation by surgery. Highly matured judgment should be invoked in making this seemingly simple decision. If the locus of the disease because either of deep seatedness or its generalization does not admit of the complete removal of all diseased tissue, do nothing except palliate. To operate in such a case will surely produce malignant recurrence and hasten the death of the patient. If the locus of the disease does admit of the complete removal of all diseased tissue, an operation should be resorted to immediately, and if properly performed will probably result in a complete cure.

CASE REPORT.—In March, 1925, I was consulted by a man twenty-six years old and six feet tall who weighed 210 pounds. He asserted he was in excellent health until two years before when he first noticed a small, hard, painless lump near the angle of the jaw in right side of neck. This mass enlarged slowly without symptoms during the succeeding sixteen months until it attained the size of a bird's egg and he consulted a physician who attributed the enlargement to tonsillar infection or infected teeth. In the month following, August, 1924, seven months previous to the date I was consulted, a tonsillectomy was performed and an impacted tooth and three or four other teeth were removed, all without any apparent beneficial consequences. To me he complained of weakness and loss of appetite and he called to my attention a tumor in the right side of his neck. This tumor, of the size of a walnut, was hard, slightly irregular, rather freely movable, and not adherent to the skin, and gave no evidence of either redness or œdema. A careful search failed to reveal a primary tumor in mouth, pharynx, or elsewhere. I noted the lower cervical claim and posterior cervical glands were enlarged to the size of marbles and that the supraclavicular glands were palpable. An X-ray of the chest disclosed some enlargement of the hilus and bronchial nodes. The Wassermann reaction was negative. The urine was negative. Blood showed moderate anemia; Hæmoglobin 80 per cent.; leucocytes 8000; polymorphonuclears 80 per cent.; small lymphocytes, 14 per cent.; large lymphocytes, 4 per cent.; eosinophiles 1 per cent.; and transitionals 1 per cent. Temperature 98; pulse 76; respiration 20. March 13, 1925, under gas anæsthesia, a gland was removed for pathological study. A diagnosis of "Primary Endothelioma of Cervical Lymph-nodes" was made.

In the subsequent course of the disease the patient lost weight and strength, suffered from shortness of breath, and an annoying cough that was attended by expectoration of mucopurulent blood-tinged sputum, and ultimately a metastasis to the left breast developed, though no metastasis to the abdominal cavity ever took place. X-ray picture of his chest made several weeks after the diagnosis showed the metastasis more advanced than in the previous X-ray of his chest made previously thereto. The patient received X-ray treatments but the disease progressed steadily without any apparent retardation from this source. He died in September, 1925, two years and six months after the first small, hard, discrete nodule was noted in the right side of his neck. Although an autopsy was urged, the family objected seriously, and it was not performed, which, from the scientific viewpoint is unfortunate.

CONCLUSIONS

(1) Primary endothelioma of the cervical lymph-nodes is a more common neoplasm than is generally supposed.

(2) The disease is limited to one or a small group of glands, more com-

monly the superficial cervical lymph-nodes of the anterior triangle than the more inaccessible cervical glands.

(3) Biopsy is the only reliable method of diagnosis at this time and even that requires the services of a highly competent pathologist.

(4) A suspicious tumor of the neck should always be subjected to biopsic diagnosis early in its development.

(5) Primary endothelioma of the cervical lymph-nodes is now a pathological entity and should become a clinical entity.

(6) If an early diagnosis of primary endothelioma of the cervical lymph-nodes is once definitely made and it is determined same is not the generalized form, an operation should be resorted to immediately, and if properly performed will probably result in a complete cure.

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